Met-APs, caspases and separases. For example, the cleavage specificity of calcium-activated proteases called calpains and the properties of other, less well characterized cytosolic and/or nuclear proteases suggest that they, too, may function as upstream components of the N-end rule pathway. The DIAP1 findings by Ditzel *et al.*[8] are exciting not only because of what they tell us about the link between apoptosis and the N-end rule pathway. They also suggest the existence of other caspase-produced N-end rule substrates, of which the list in Fig. 2 is just the start. These substrates remain to be identified and understood in the context of N-end rule's physiology. □

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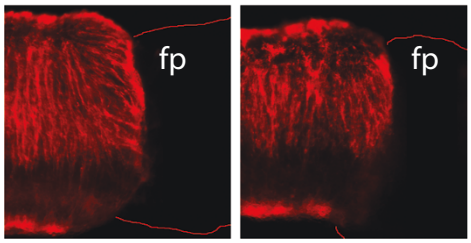
Morphogens recycled

Despite its eventual complexity, the developing nervous system seems to be directed by an elegant economy of cues. We are beginning to learn that factors can perform more than one job during its development, and in the April issue of *Cell* (**113,** 11–23 (2003)), Tessier-Lavigne and colleagues provide compelling evidence that Sonic Hedgehog (Shh), a morphogen known for its role in neural tissue patterning, also functions later to attract navigating axons.

During development of the nervous system, axons are guided by a combination of attractive and repulsive cues. In the embryonic spinal cord, a subset of axons are attracted from the dorsal neural tube towards the floor plate, where they form axon commissures. It is well established that outgrowth of these axons and their subsequent attraction towards the floor plate is directed by the long-range chemoattractant Netrin-1. However, the defects observed in *Netrin-1* mutants have hinted that residual chemoattractant activity may reside in the floor plate in its absence and raise the possibility that a second attractant is guiding the axons. Tessier-Lavigne and colleagues now show that this second signal is provided by Shh. Interestingly, unlike Netrin-1, Shh cannot function as a permissive factor to stimulate the outgrowth of these axons *per se*, but seems to be important both *in vitro* and *in vivo* for their subsequent routing.

The authors find that both COS cells and tissue explants expressing Shh, similarly to those expressing Netrin-1, can reorientate commissural axons. The chemoattractant effects of Shh seem to require Smoothened (Smo; see figure), a transmembrane protein known to function downstream of Shh in other contexts. To exclude the possibility that Shh might affect guidance indirectly, they also confirmed that it cannot induce repatterning of older spinal cord tissue in which the axons grow, as it can earlier in development. Moreover, they showed that applying a soluble source of Shh close to growing axons in culture was sufficient to trigger axon turning, an effect that also required Smo activity.

Finally, they asked whether Shh signalling is required *in vivo*. Using the Cre-LoxP recombinase system, they selectively



Smo activity in the floor plate. *Netrin-1*-mutant floor plate attracts commissural axons, revealing a second chemoattractant from the floor plate (left). Cyclopamine, an inhibitor of Smo, inhibits the Netrin-independent activity of the floor plate, indicating that Shh signalling is required for this activity (right). fp, floor plate. Reprinted from Charron *et al.* 113, 11–23 © (2003) with permission from Elsevier.

disrupted Smo function in subsets of dorsal spinal cord cells, including commissural neurons, and showed that this results in defects in axon guidance. Importantly, this suggests that the Shh signal is required autonomously in the commissural neurons themselves.

Together, these findings show that in addition to its earlier role in directing ventral tissue patterning, Shh functions later as a chemoattractant, guiding axons towards the floor plate. This adds to a rapidly growing list of factors that are re-used by the embryo for diverse functions during development. We know that another family of morphogens, the bone morphogenetic proteins (BMPs), which pattern the dorsal spinal cord, function later to repel commissural axons away from the dorsal midline. So a model begins to emerge where Shh and BMPs, which initially cooperate during patterning along the dorsoventral axis, pair up again to lend commissural axons a guiding hand.

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